



微生物降解磺胺甲恶唑的研究进展

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摘要: 抗生素是一类难降解、低浓度就有高生态毒性效应的化合物, 近年来被归为新型环境污染物, 其环境残留与去除备受关注。作为广泛使用的抗生素之一, 磺胺甲恶唑在水土环境中的残留量不断增加, 检出率也越来越高。研究表明, 磺胺甲恶唑是少数几种可被微生物降解的抗生素之一, 微生物降解法是最具潜力的残留磺胺甲恶唑去除手段。本文总结了磺胺甲恶唑在土壤、沉积物、活性污泥、混合菌群、酶等条件下的降解及已分离的具有降解能力的单菌株对磺胺甲恶唑的降解情况, 包括其降解效率、降解条件等, 归纳了目前磺胺甲恶唑微生物降解的主要分类, 并讨论了影响磺胺甲恶唑降解的两个特有因素。指出从分子生物学及生物信息学角度研究其降解途径, 降解菌、降解菌群的人工构建及其在含磺胺甲恶唑污水处理中的应用与效果评价等应为今后磺胺甲恶唑生物降解与应用研究的重点。

关键词: 磺胺甲恶唑, 抗生素, 微生物降解, 新型污染物, 降解机制

随着社会发展和各种需求的不断增加, 抗生素在生活中的应用越来越广泛, 尤其是在畜禽及水产养殖行业(约 84%)^[1], 导致其在环境中的累积残留引发了越来越多的环保问题, 不仅能直接对暴露在环境中的动植物产生毒害作用, 更严重的是改变原有的环境菌群结构, 筛选出具有抗药性的菌, 还能促进抗药基因的产生、传播^[2]。抗生素与抗药基因、抗药菌一起构成新的污染体系, 互相联系, 错综复杂, 是环境修复面临的一大难题。

磺胺甲恶唑(Sulfamethoxazole, SMX), 又名新诺明, 是一种磺胺类的广谱抗生素, 纯品为白色结晶粉末, 无臭, 味微苦, 难溶于水、易溶于酸碱, 结构式如图 1 所示。因其在结构上类似对氨基苯甲酸(PABA), 可与 PABA 竞争作用于细菌体内的二氢叶酸合成酶, 阻止细菌二氢叶酸的合成, 从而抑制细菌的生长繁殖^[3]。主要用于治疗泌尿道感染以及禽霍乱等, 对革兰氏阳性菌和革兰氏阴性菌都有良好的抑菌效果, 目前广泛应用于

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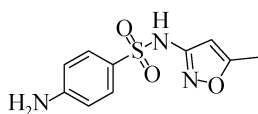


图 1. 磺胺甲恶唑的化学结构

Figure 1. Chemical structure of sulfamethoxazole.

人类、畜禽、水产养殖作物等领域。然而由于大量使用, SMX 在环境中的残留问题日渐严重, 不仅在环境中的检出率非常高, 其累积量也越来越多, SMX 在水环境中长期存在会对水生生物有严重的危害, 对藻类的危险系数 $>7^{[4-5]}$ 。据报道, SMX 在中国北方土壤中的残留量达到 0.9 mg/kg, 粪肥中的残留量高达 5.7 mg/kg, 而且在使用过粪肥助长的蔬菜中也检测到 SMX^[6]。在河流及地表水中 SMX 的含量也处于较高水平, 西班牙略夫雷加特河河水中, SMX 残留量高达 1.49 $\mu\text{g/L}^{[7]}$, 甚至研究人员从中国东部经过处理的饮用水中都检测到 SMX, 而这些饮用水的源头是中国第一大河长江^[8]。另外, 2017 年 10 月 27 日, 世界卫生组织国际癌症研究机构公布的致癌物清单初步整理, SMX 名列 3 类致癌物清单中。因此, 水环境中 SMX 的残留成为人类及其他动植物健康的一大隐患, 而有效去除也逐渐成为人们热切关注的焦点。

目前, SMX 的降解主要集中在物理法(光降解、热降解等)、化学法(芬顿氧化、电化学等)及微生物法。物理或者化学法不仅成本高昂, 操作复杂, 而且往往只是通过转化、修饰等途径把 SMX 转变成毒性较小、抑菌效果不明显的化合物, 而这些化合物通常是比较稳定的复杂化合物, 并不能参与自然界的物质循环, 易造成环境中的累积, 久而久之会成为自然环境的潜在威胁。相比之下, 微生物降解法优势明显, 操作简单, 价格低廉, 环境友好, 没有二次污染^[9], 且已发现能把 SMX 矿化的菌群^[10-11], 使得微生物降解法成为非常具

有潜力的一种抗生素去除途径。自本世纪初以来, SMX 的微生物降解研究开始被广大科研工作者关注, 不到 20 年时间里, 已有很多文献报道了 SMX 在微生物的作用下而降解、代谢或者矿化。

然而, 纵观这些文献, 大多都是用活性污泥、土壤、沉积物以及混合菌群来降解 SMX, 在这种复杂的降解过程中, 很难了解 SMX 具体是怎么进行转化、代谢的, 更不能掌握在其微生物降解过程中所涉及的酶、关键基因等信息, 阻碍了对微生物降解 SMX 的进一步认识和理解。相比之下, 用可培养微生物来降解的研究起步较晚, 报道较少。目前的报道主要集中在 SMX 降解菌筛选、降解产物解析、降解动力学研究以及降解条件优化; 而从酶学、分子层面、基因层面去研究其降解机制、代谢途径的报道寥寥无几。这也是为什么 SMX 降解方法不少, 但真正实际运用的却不多的重要原因之一。因此, 在这个分子生物学迅速发展的时代, 更应注意详细解析 SMX 微生物降解机制的重要性, 以期为实际应用打下坚实的理论基础。

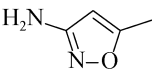
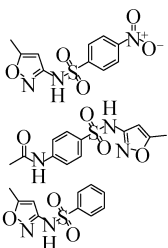
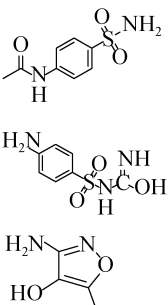
本文详细描述了科研工作者对 SMX 微生物降解的报道, 总结了用土壤、沉积物等自然条件, 各种生物反应器中的活性污泥, 混合菌及纯菌, 还有各种功能酶对 SMX 的降解效率及条件; 归纳了目前已经报道的 4 种 SMX 降解方式; 探讨了可能影响 SMX 降解的两个独特因素并指出以后该领域以后科研工作的重点。

1 土壤、沉积物等自然条件下 SMX 的降解

在自然条件下, 残留的 SMX 也能在微生物、光照、水、热等一系列条件下实现降解(表 1)。但是在不同种类、质地的土壤中有不同的降解速率

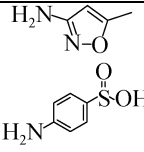
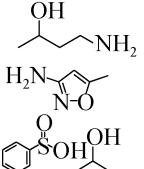
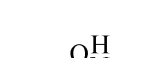
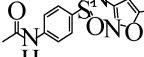
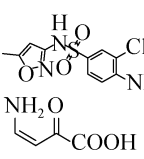
表 1. 菌群及酶对 SMX 的降解

Table 1. SMX degradation by microbial floras and enzymes

Microbialfloras /Enzyme	Degradation process	Initial concentration	Removal rate or efficiency	Time	Oxygen demand	Degradation products	References
Sludge	Sequencing Batch Reactor (SBR) activated sludge	383 mg/L	100%	3 h	Aerobic	-	[16]
	Photo-Fenton pretreatment followed by a Sequencing Batch Biofilm Reactor	200 mg/L	nearly 100%	48 h	24 h Aerobic/ 24 h Anoxic	mineralized	[17]
	Biosolids	100 µg/L	100%	2 d	Anoxic	-	[18]
	Activated Sludge Process	100 µg/L	17.1%	48 h	Aerobic	-	[19]
	Internal loop photobiodegradation reactor (ILPBR)	120 mg/L	100%	8 h	-	-	[20]
	Anaerobic packed and structured-bed reactors	400 ng/L	(83%±12%)–(85%±10%)	12 h	Anaerobic	-	[21]
	Sulfatereducing bacteria (SRB) sludge	100 mg/L	13.2±0.1 mg/(L·d)		Anoxic	-	[22]
	Activated sludge	10 mg/L	100%	14 d	Aerobic		[23]
	Activated sludge cultures	10 mg/L	100%	8 d	Aerobic	-	[24]
	Sequencing Batch Reactor sludge	10–40 mg/L	59%–100%	8–41 d	Anaerobic	-	[25]
	Sludge	272 µg/L	27 µg/(L·d)	190 h	Aerobic	-	[26]
	Bioelectrochemical	30 mg/L	>95%	21 h	-	-	[27]
	Sequencing Batch Reactor	100 µg/L	86% 98%	6 h 24 h	Aerobic		[28]
	Granular and Suspended Activated Sludge Processes	2 µg/L	84% in granular, 73% in suspended biomass	12 h	Anoxic/anaerobic/oxic	-	[29]
	Rotating biological contactor (RBC)	5 to 120 mg/L	80.3%–89.4%	60 h	Aerobic	-	[30]
	Swine sludge	2 mg/L	100%	2 d	Anaerobic	-	[31]
			faster when added lactate, citrate, especially sucrose				
	Laboratory scale membrane bioreactors	750 µg/L	65% in average	2 d 50 d 30 d	Aerobic DO=0.5 mg/L DO>2 mg/L	-	[32]
	Microbial fuel cells(MFC)	0.04/0.08/0.20/0.39/ 0.79 mmol/L	0.67/1.37/3.43/7.3 2/13.36 µm/h		Anaerobic		[33]

(待续)

续表 1

	Microbial fuel cell (MFC) reactors	20 ppm 200 ppm	100% 100%	3 d 96 h	Anaerobic		[34]
	Microbial fuel cell	20 ppm	85%	12 h	Anaerobic		[10]
Sediments	Mangrove sediments	10 mg/kg	100%,	30d	Anaerobic		[14]
	Water-sediment system of a natural river	20 mg/kg 15 mg/L	90.1% in sediment 86.8% in water	– –	– –		[12]
Soils	Manure-amended soils	10 mg/kg	>50%, in clay loam >80%, in loam soil	20 d 20 d	Faster in anaerobic than aerobic	–	[13]
	Soil	4 mg/kg	(7.6%±0.3%)– (6.8%±0.8%)	84 d	–	mineralized	[15]
	Artificial composite soil treatment system	5 mg/L	70%	10 d	–	–	[35]
	Artificial composite soil treatment systems	15–30 µg/L	<80%	1 h	–	–	[36]
	Non-sterile soil	10 mg/kg	50%	2 d 7 d	Aerobic Anoxic	–	[37]
	Laboratory columns/soil column test system	0.25 mg/L	60% 0	14 d	Aerobic Anoxic	–	[38]
Consortium or biomass	Mixed consortium of bacteria	6 mg/L	(47%±1.2%)– (55%±0.2%)	300 h	Aerobic	–	[39]
	Manganese-adapted aerobic biomass	2 mg/L	>98%	2 d	Aerobic	–	[40]
	Horizontal-flow anaerobic immobilized biomass reactor	40 µg/L	97%	24 h	Anaerobic	–	[41]
Enzymes	A heme peroxidase, chloroperoxidase (CPO)	15 µmol/L	98.64%	20 min	–		[42]
	Anaerobic sludge enzymes	0.1 ng/µL	>20%	72 h	Anaerobic	–	[43]
Others	A municipal sewage treatment plant	20 mg/L	100%	50 d	Aerobic	–	[44]
	Biofloculant MFX	1 mg/L	>60%	12 h	Aerobic	–	[45]
	Spent mushroom compost (SMC)	200 mg/kg	50%	1.3 d	Aerobic	–	[46]

且容易受环境因素的影响, Yang 等发现在壤质土中 SMX 的降解效果要明显优于粘壤土和壤砂土, 初始浓度为 10 mg/kg 时, 20 天内降解效率分别为 80%、50%、50%以上。而用水-沉积物去除 SMX

时, 其降解效果受到温度及腐殖酸浓度的严重影响^[12-13]。另外, 在这种条件下 SMX 的降解通常极其缓慢且不易稳定进行, 而在人工干预进行强化后其降解效率大大提高, Chuwen Yang 等利用红

树林沉积土为降解介质, 10 mg/kg 的 SMX 在不同地区的土壤以及不同的季节里的降解效果差异较大, 在春季需要 10–25 d 能降解完全, 在秋季 30 d 的降解效率为 40%–60%。加入一定量的蔗糖后, 在春季和秋季的完全降解时间分别变为 5–15 d 和 20–30 d^[14]。Juying 等用未添加过肥料的农业土壤去研究其对 SMX 的降解发现, 不经过人工干预的土壤对 4 mg/kg 的 SMX 完全降解需要 80 d 以上, 而在加入 5%–10% 的生物固体后其降解效率明显提升^[15]。

总的来说, 这些方法对 SMX 的去除效率与强度很容易受到土壤理化性质的干扰, 其稳定性与持久性都不能保证, 如果能针对性地加入 SMX 降解菌剂或者进行生物强化, 其降解效率和强度都会进一步加强。

2 生物反应器中活性污泥对 SMX 的降解

在传统的污水处理过程中, 活性污泥起到不可估量的作用。它对污水中有机污染物的吸附、降解有着重要的意义, 可以说活性污泥是污水处理技术的灵魂。因此, 在 SMX 的微生物降解过程中, 污泥法研究得最多, 配合各种各样的生物反应器(如序批式好氧反应器、生物膜反应器、微生物燃料电池等), 在不同的温度、pH、外源碳的添加与否等条件下, 从厌氧、兼氧到好氧以及好氧厌氧交替使用情况下, 都实现了 SMX 的高效降解(表 1)。SMX 初始浓度从 400 ng/L 到 383 mg/L, 大部分都能在 2 d 内实现 80% 以上的去除。尤其是 Drillia 等报道的序批式生物反应器在好氧条件下, 能在 3 h 内将浓度高达 383 mg/L 的 SMX 降解完全^[16], 实现了高浓度 SMX 的快速、高效去除。

3 已分离菌对 SMX 的降解

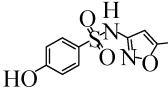
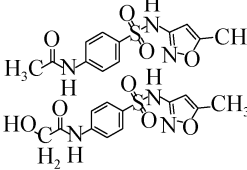
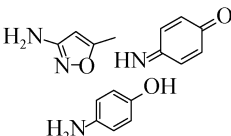
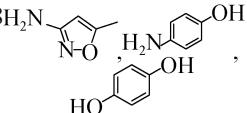
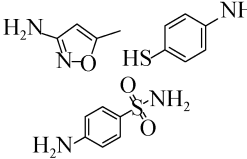
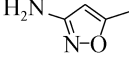
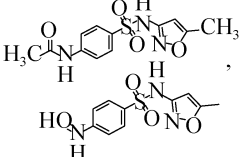
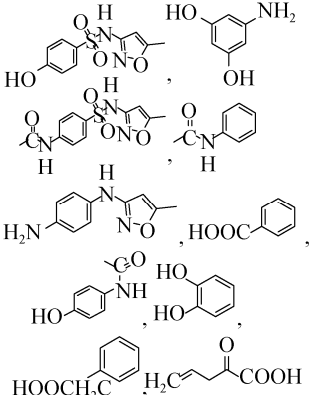
3.1 混合菌对 SMX 的降解

随着磺胺甲恶唑微生物降解被日渐关注, 研究者将目光从复杂环境投向混合菌以及纯菌, 可以利用几种不同的菌对 SMX 进行分步降解, 最后彻底矿化或者形成微生物容易利用的小分子物质。Ana C. Reis 等发现 SMX 降解菌 *Achromobacter denitrificans* PR1 在单独行使降解功能的时候并不稳定且效率低, 而当该菌与 *Leucobacter* sp. GP 混合培养时, 对 SMX 的降解能力稳定又高效^[47]。Xin 等发现 SMX 能够抑制 *Pycnoporus sanguineus* 菌产生的漆酶活性, 使得漆酶对 SMX 降解效率变低, 而当把 *Pycnoporus sanguineus* 和 *Alcaligenes faecalis* 菌混合培养时, SMX 降解效率大大提升^[48]。我们实验室也曾对降解 SMX 的富集菌群进行分离培养, 从中分离获得了包括 SMX-R2A-1~6、SMX-1~3、SMX-LB-1、3A5MI-R2A-1 等 20 多株的细菌, 并确定了 SMX-R2A-2 (*Paenarthrobacter* sp.)、SMX-LB-1 (*Arthrobacter* sp.) 菌株对 SMX 具有降解效果。

3.2 单菌株对 SMX 的降解

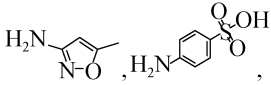
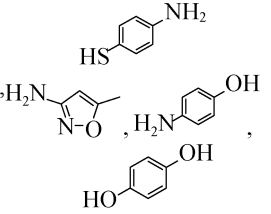
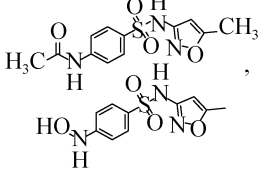
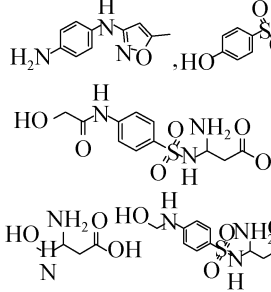
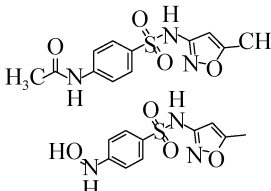
如表 2 所示, 纯种微生物对 SMX 的降解主要有细菌、真菌和绿藻, 这些微生物可通过生长代谢或共代谢的方式对 SMX 进行转化或部分降解, 而能彻底降解/矿化 SMX 的菌株少见报道。研究较多的主要是细菌对 SMX 的降解, 包括革兰氏阴性和阳性细菌都对 SMX 具有转化/降解的能力。从分类学上看, 绝大多数 SMX 降解菌都属于变形菌门和放线菌门, 厚壁菌门中只有 2 株希瓦氏菌具有 SMX 降解功能^[49]。在属水平上, 30 株不同

表 2. 纯菌株对 SMX 的降解
Table 2. SMX degradation by isolated strains

Classification	Strains	Initial concentration	Degradation rate, time and oxygen demand	Degradation products	References
Actinobacteria	<i>Rhodococcus rhodochrous</i> (ATCC13808)	30 mg/L	20%, 35 days, aerobic		[55]
	<i>Rhodococcus equi</i> (ATCC 13557)	6 mg/L	29%, 120 h, aerobic		[56]
	<i>Microbacterium</i> sp. JN196543	0.5 mmol/L	52%, 12 h, aerobic	CO ₂	[57]
	<i>Rhodococcus</i> sp. JN196542			–	[58]
	<i>Tsukumurella</i> sp. JN851820			–	[58]
	<i>Microbacterium</i> sp. HF571532	10 mg/L	1.0–1.7 mg/L/d, 10 days, aerobic	–	[59]
	<i>Microbacterium</i> sp. HF571537		More faster in R2A-UV and MSM-CN media	–	[59]
	<i>Microbacterium</i> sp. strain BR1	0.5 mmol/L	100%, 1 h, aerobic		[60]
Proteobacteria	<i>Gordonia</i> sp. SMX-W2-SCD14	5 mg/L	45.2%/62.2%/51.4%, h, aerobic		[61]
	<i>Pseudomonas psychrophila</i> HA-4	100 mg/L	34.30%, 192 h, aerobic		[62]
	<i>Achromobacter denitrificans</i> PR1	600 μmol	73.6±9.6 μmol SMX/g cell dry weight 100%, 40 h, aerobic		[63]
	<i>Alcaligenes faecalis</i> CGMCC 1.767	50 mg/L	>80%, 16 h, aerobic, 100 mg/L of exogenous VC, VB6 and GSSG enhanced SMX bioremoval		[64]
	<i>Enterobacter cloacae</i> T2	100 mg/kg	84.14%, 30days, aerobic		[49]

(待续)

续表 2

	<i>Shewanella oneidensis</i> MR-1 <i>Shewanella</i> sp. strain MR-4	10 mg/L	59.88%±1.23% and 63.89%±3.09%, 5 days, aerobic		[60]
	<i>Ochrobactrum</i> sp. SMX-PM1-SA1, <i>Labrys</i> sp. SMX-W1-SC11	5 mg/L	45.2%/62.2%, 288 aerobic		[65]
	<i>Alcaligenes faecalis</i> CGMCC 1.767	50 mg/L	90%, 24 h, aerobic		[66]
	<i>Acinetobacter</i> sp. W1	5–240 mg/L	100%, 50 h, aerobic		[57]
	<i>Achromobacter</i> sp. JN196540 <i>Achromobacter</i> sp. JN196541 <i>Ralstonia</i> sp. JN196539 <i>Ralstonia</i> sp. JN196538	0.5 mM	52%, 12 h, aerobic	CO ₂	[58]
Fungus	<i>Brevundimonas</i> sp. HF571531 <i>Pseudomonas</i> sp. HF572913 <i>Pseudomonas</i> sp. HE985241 <i>Pseudomonas</i> sp. HF571533 <i>Pseudomonas</i> sp. HF571535 <i>Pseudomonas</i> sp. HF571536 <i>Variovorax</i> sp. HF571534	10 mg/L	1.0–1.7 mg/(L·d), 10 days,– aerobic More faster in R2A-UV and MSM-CN media		[67]
	<i>Trametes versicolor</i> ATCC 42530 and <i>Bjerkandera adusta</i> ATCC 28314	25 mg/l	90–94%, 30 days,– anaerobic		[50]
	white-rot fungus <i>Phanerochaete chrysosporium</i>	10 mg/L	74%, 10 days, aerobic	–	[68]
	<i>Pleurotus ostreatus</i>	50 mg/l	74%, 15days	–	[48]
	<i>Pycnoporus sanguineus</i> and <i>Alcaligenes faecalis</i>	50 mg/L	>93%, 24 h, aerobic		[64]
Alga	Fungal endophyte Z3	100 mg/kg	57.64%, 30days, aerobic	–	[69]

细菌来自 15 个属，其中出现频率较高的有假单胞属 (*Pseudomonas* sp.) 为 6 株，细杆菌属 (*Microbacterium* sp.) 为 4 株，红球菌属 (*Rhodococcus* sp.)、无色杆菌属

(*Achromobacter* sp.) 各 3 株，产碱杆菌属 (*Alcaligenes* sp.)、罗尔斯通菌属 (*Ralstonia* sp.) 和希瓦氏菌属 (*Shewanella* sp.) 各 2 株。6 株真菌除了一株未知分类

外,另外5株分别为烟管菌属,侧耳属,密孔菌属,栓菌属和平革菌属。仅有的1株绿藻为四链藻属。从SMX的降解类型来看,产碱杆菌属和红球菌属细菌更倾向于对SMX进行修饰转化,而罗尔斯通菌属、希瓦氏菌属和无色杆菌属细菌更倾向于将SMX降解为小分子化合物,大多数真菌的降解产物并未被鉴定出来。另外,这些纯培养微生物对SMX的降解大多都是在好氧条件下进行的,外加碳源或者维生素会明显提升其降解效率。在真菌界中,白腐真菌(white-rot fungi)在抗生素降解中发挥着重要作用,不仅对SMX有降解效果^[50],对四环素及土霉素^[51]、氟喹诺酮类药物环丙沙星^[52]、正定霉素^[53]甚至对农药炔咪菊酯(imiprothrin)、氯氰菊酯(cypermethrin)、卡巴呋喃(carbofuran)都有一定的降解效果^[54],而这些降解机制往往都与它们分泌的漆酶有关,意味着这一类菌在环境微生物修复方面有良好的应用前景。

4 SMX的降解酶及其酶学研究

由于SMX微生物降解的研究起步较晚,在酶学、基因层面的研究鲜有报道。目前,已知的对SMX具有降解、转化作用的酶有三种:单加氧酶、来源于真菌的漆酶以及过氧化物酶(来源于一株 *Caldariomyces fumago*),另外 Gonzalez-Gil 等用厌氧污泥中存在的混合酶来处理SMX,也有降解效果^[43]。Benjamin Ricken 等分离到一株 *Microbacterium* sp.的菌株能以SMX为唯一碳源进行新陈代谢。该细菌中有一个基因簇发挥了降解功能,这个基因簇由3个功能基因组成,其中两个单加氧酶基因(*sanA*, *sadB*)和一个 NADH^+ 还原酶基因(*sadC*),通过SadA和SadB酶的作用,在 FMNH_2 辅助下SMX最终生成3-氨基-5-甲基异恶唑(3A5MI)、偏苯三酚和 SO_2 ^[59,70-71](图2),这也是目前为止仅有的从生物化学层面和分子生物学层

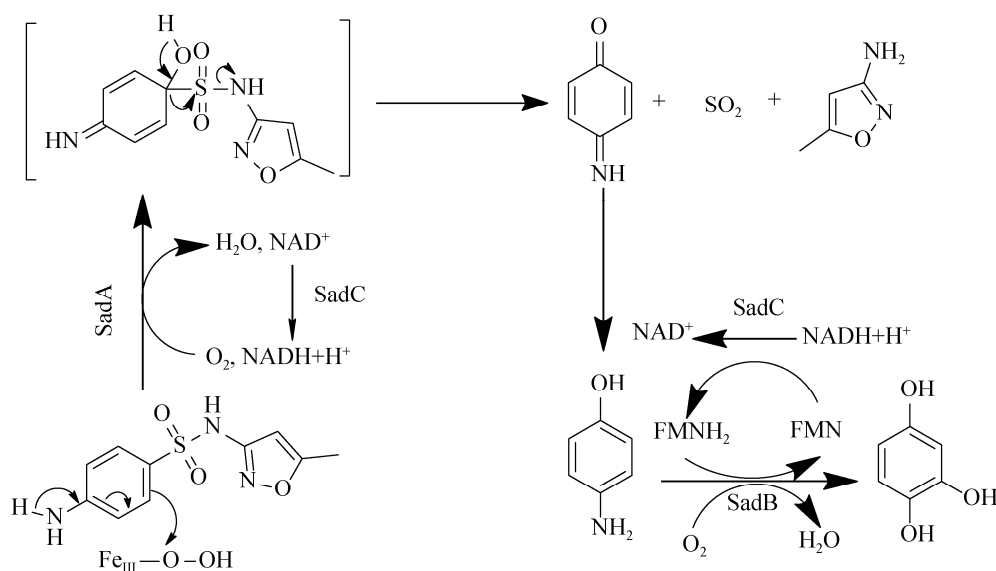


图2. 已验证的SMX降解途径及需要的酶^[59,70-71]

Figure 2. Pathway and enzymes for SMX degradation^[59,70-71].

面都进行验证过的文献报道。此外, 该基因簇在放线菌中普遍存在且在该基因簇附近又发现转座子释放酶, 这说明这种 SMX 降解机制可能在环境中普遍存在。漆酶对 SMX 的转化降解往往发生在真菌中, 从效果上看漆酶的活性与 SMX 的降解效率具有很强的相关性^[50,68], 然而其降解机理并不清楚。氯化物过氧化物酶对 SMX 的降解只有 Xiao 等^[42]研究过, 它可对 SMX 进行氯化修饰, 对异恶唑环的打开也有着很好的效果, 但是研究人员直接用酶去降解, 其运行条件比较严苛, 也并不清楚能生产该酶的菌对 SMX 的降解效果。

相比于已经发现报道的 SMX 降解菌株资源, 其降解功能酶以及基因的深层次研究显得少之又少, 尤其是从分子生物学的角度对这些代谢通路研究的缺乏使得我们对细菌降解抗生素的过程缺乏足够的了解和认识。

5 SMX 的微生物降解方式

目前已检测到的 SMX 降解或转化主要有 4 种方式(如图 3, 其中红色标注的是常见的代谢产物), 首先是苯环与异恶唑环的断裂, 能形成 3A5MI、对氨基苯酚、对苯二酚、对巯基苯胺或者对氨基苯磺酸等物质, 这是 SMX 降解最常见的一种形式, 其中 3A5MI 也是最常见的降解产物^[55,61,71]。第二种转化方式是苯环上氨基的修饰或者去除, 乙酰化和羟基化是最常见的修饰方式, 粪产碱杆菌对 SMX 的转化往往都是通过这两种修饰方式进行转化^[48,63,65]。还有些菌株可以将 SMX 苯环上的氨基转换为羟基或者直接去掉, 或者更复杂的修饰, 而部分菌株能在这种转化方式的基础上再进行降解, 最终生成分子量较小、容易利用的化合物。但也有很多菌并不能真正意义上降解 SMX,

而只是简单层次的转化修饰。第三种降解方式是对异恶唑环的作用或者对异恶唑环和苯环同时进行修饰, Shizong 等^[66]报道了菌株 *Acinetobacter* sp. W1 能在修饰 SMX 苯环氨基的同时将异恶唑环打开, 然后再将这两部分断开, 这是一种比较少见的降解方式。由于异恶唑环比较稳定、难降解, 因此这种方式或许能给 SMX 的重要降解中间产物 3A5MI 的进一步降解提供思路。最后一种是苯环和异恶唑环之间连接键的变化, 直接脱掉 1 个硫原子和 2 个氧原子, 这种方式仅有一例报道且是根据降解产物荷质比对产物结构的猜测, 并不具备普遍性。

6 影响降解的因素

众所周知, 温度、pH、溶氧量、孵育时间、底物初始浓度以及外源碳、氮的添加都会影响细菌的生长繁殖, 进而影响降解菌株在降解过程中的效率及强度, 这些也都是之前研究比较关注的点。然而抗生素物是一种特殊的污染物, 它的降解不光受到这些方面的影响, 如 SMX 的降解与氨氧化过程及抗药性也有着千丝万缕的联系。

6.1 氨氧化过程对 SMX 降解的影响

很多污水处理厂、畜禽养殖污水处理工艺等在处理含有较高含量 SMX 污水的过程中, 并没有特别添加 SMX 降解菌剂, 但是往往都能取得不错的效果^[44]。经研究发现, 氨氧化细菌(AOB)和氨氧化古菌(AOA)与 PPCPs (pharmaceutical and personal care products)的降解去除有密切关系^[72-73]。2016 年 Kassotaki 等发现, 氨氧化效率的提升可以促进 SMX 的去除效率。在具有硝化功能的 SBR 反应器中, SMX 的去除效率能达到 98%, 而当反应器中

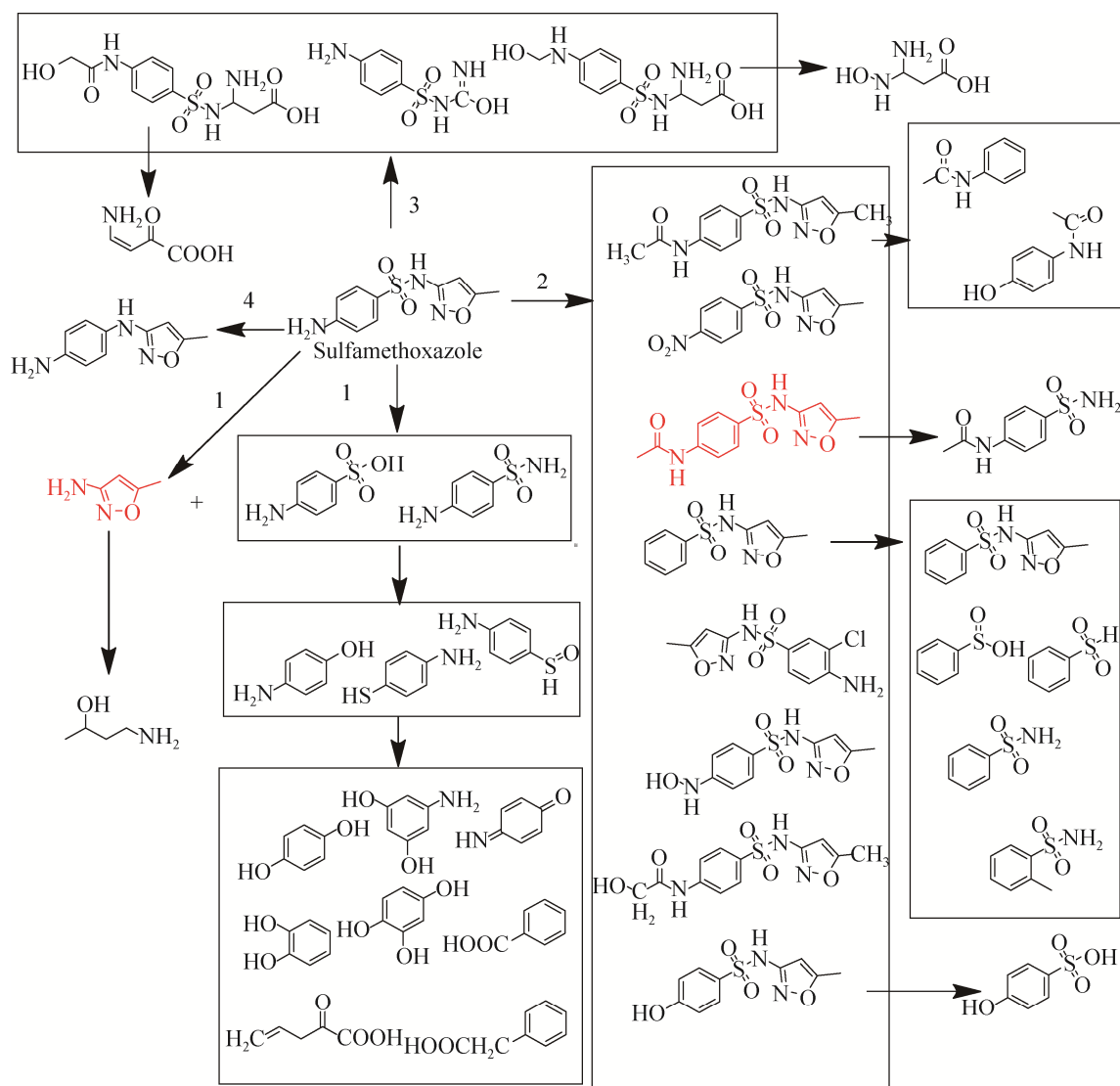


图 3. 已检测到的 SMX 降解或转化方式

Figure 3. Degradation types of SMX degradation or transformation.

加入氨氧化抑制剂(烯丙基硫脲)后, SMX 的去除效率直接降为 0%^[28]。由此可见, 氨氧化作用与 SMX 的降解过程甚至是有机的降解过程都有着千丝万缕的联系, 但是到底这两者之间是如何影响、如何制约的, 还需进一步研究。

6.2 耐药性与降解作用之间的关系

抗生素是一类能对微生物生长起到抑制作用的化合物, 而在降解过程中这些化合物要对微生物起到促进生长的作用, 这也是抗生素降解最难

的地方。一般认为, 抗生素降解菌是肯定能耐受抗生素的这一命题才合乎情理, 即对该抗生素有耐药性才能对进一步降解。然而, 有研究发现, 4 株 *Klebsiella pneumoniae* 和 1 株 *Escherichia fergusonii* 能利用氯霉素作为唯一碳源能源进行生长, 但是药敏试验发现这些菌株对氯霉素是敏感的^[74], 这表明细菌的耐药过程和降解药物过程是两个独立的途径。而又有报道指出, 在具有抗药性的菌中, 更容易找到能利用该抗生素的表

型^[75], 这意味着抗药性或许对降解过程具有促进作用。那么它们之间到底有没有相关性, 或者互相促进、调控的作用, 这仍然是一个谜团。

对于 SMX, 目前已知的抗性基因主要是 *sul1*、*sul2* 和 *sul3*, 它们在降解细菌中的存在或者拷贝数的多少和降解菌对 SMX 的降解效果、效率之间的关系是一个很有意思的方向, 需要进一步的研究。

7 总结和展望

随着近年来环境中残留抗生素、抗性基因和抗药菌被称为新型污染体系, 用微生物的方法降解抗生素越来越受到大家的关注, 尤其是磺胺类药物 SMX 的微生物降解, 已经有很多的科研工作者发现、分离了众多降解菌株。然而, 我们应该看到虽然降解菌株资源不断丰富, 但是绝大多数科研工作都太过局限于菌株的分离和降解条件的优化, 我们对具体的降解途径却知之甚少。迄今为止, 只有一篇报道研究了 SMX 在降解过程中涉及的基因和酶, 相比众多且复杂的降解途径来说, 这方面的知识显得非常有限。而代谢途径不清楚, 则无法详细了解降解过程, 更无法将抗生素的微生物降解进一步挖掘和利用。因此, 代谢途径的具体阐释及相关基因、酶的探究将会是该研究方向的重要目标。随着生物信息时代的到来, 尤其是近年来组学分析、高通量测序等技术飞速发展, 已经有很多科研工作者将目光投向了用基因组学的方式去探索、解释微生物对 SMX 的降解及转化, 阅览近年来的文献可以明显看到降解细菌的基因组学分析、转录组学、代谢组学分析不断出现, 这将非常准确高效地指导我们对抗生素降解菌资源的进一步开发利用, 其中有用的基因、酶

等关键信息都将被一一揭示出来, 相信在不远的将来, 广大科研工作者必将找到能高效、合理降解抗生素的优质方法。

另外, SMX 的大部分降解产物都检测到 3-氨基-5-甲基异恶唑, 后者是一个环境毒性较 SMX 小的化合物, 也具有一定的抗菌效果, 化学性质比较稳定, 并不容易被微生物降解, 受到科研工作者的关注较少, 其微生物降解的报道很少见。Lu Wang 等发现在微生物燃料电池中, SMX 被降解成 3A5MI, 而 3A5MI 可进一步降解成 4-氨基-2-丁醇^[10,44]。另外, 也有报道发现 SMX 可以先发生异恶唑开环反应再与苯环断裂的降解过程, 然后直接生成直连化合物^[22,68]。但这些研究都只是根据质谱鉴定 *m/z* 值进行的产物预测, 并没有直接证据证实其中发生的降解途径, 其中的详细讲解途径和过程并不清楚, 这也是往后 SMX 降解研究过程的一个难点。

磺胺甲恶唑作为一类广谱抗菌药物, 其降解过程必然不同于其他传统的有机污染物, 尤其是其抗药过程和降解过程这两者之间的联系将是一个非常有意思的研究方向。另外, 在找到降解功能基因的基础上, 研究其降解途径的调节机制, 使其最大化地发挥降解功能, 在抗菌药降解菌资源的挖掘和应用上有重要的意义。最后综合工艺使用上的优化参数, 将这些抗生素降解菌应用到实际的环境修复当中去, 才能使得这些微生物资源得到良好的利用。

本实验室长年致力于有机污染物及难降解污染物的微生物降解, 目前已经分离得到了 1 株能高效降解 SMX 和 1 株能高效降解 3A5MI 的细菌, 其中 SMX 降解菌 SMX-R2A-2 和 3A5MI 降解菌 3A5MI-R2A-2 (*Pimelobacter* sp.) 分别能在 3 天内将 50 mg/L 的底物进行彻底降解, 菌 SMX-R2A-2

的能将 SMX 降解成 3A5MI, 而菌 3A5MI-R2A-2 能将 3A5MI 彻底矿化。将这两株菌共同培养, SMX 能够彻底矿化。通过基因组测序, 我们发现菌 SMX-R2A-2 中存在一个与 *SadA*, *SadB*, *SadC* 序列相似度高达 90% 以上的基因簇, 其降解机制和途径跟之前科研工作者的报道或许一致。接下来我们将重点对 3A5MI 的功能酶、基因进行深层次挖掘, 以期找到详细的降解途径, 并计划进一步分析 SMX 降解过程和抗药过程之间的联系。结合近年蓬勃发展的微生物 3D 打印技术, 我们还希望能综合多种环境污染物高效降解菌资源, 构建能够对复杂污染物、不同类型污染物有降解效果的人工菌群, 并投入到实际应用当中。

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Progress in microbial degradation of sulfamethoxazole

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Abstract: Antibiotics are regarded as a new group of environmental pollutants in recent years because of they are difficult to degrade and highly ecotoxic even in low concentrations. More and more attentions have been paid to their residues and removals in environmental. With the wide use, sulfamethoxazole residual and the detection frequency in wastewater is increasing. As one of the few microbial degradable antibiotics, sulfamethoxazole degraded by microbes is one of the most promising methods. This article summarizes the degradation efficiency and degradation conditions of sulfamethoxazole by different soil, sediment, activated sludge, mixed flora, enzymes and isolated strains. Meanwhile, degradation pathways reported in the literature are summarized. Two specific factors affecting the degradation of sulfamethoxazole are also discussed. Finally, we look forward to the perspective of molecular biology and bioinformatics in new researches, as well as the construction of degrading bacterial consortium from different pollutants in future applications.

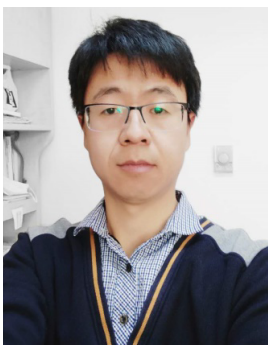
Keywords: sulfamethoxazole, antibacterial, microbial degradation, new pollutants, degradation mechanism

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